Can active surveillance really reduce the harms of overdiagnosing prostate cancer? A reflection of real life clinical practice in the PRIAS study

PRIAS Study Grp

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Original Article

Can active surveillance really reduce the harms of overdiagnosing prostate cancer? A reflection of real life clinical practice in the PRIAS study

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Contributions: (I) Conception and design: FH Drost, MJ Roobol; (II) Administrative support: FH Drost; (III) Provision of study materials or patients: FH Drost, A Rannikko, R Valdagni, T Pickles, Y Kakehi, HG van der Poel, CH Bangma, MJ Roobol, the PRIAS study group; (IV) Collection and assembly of data: FH Drost, A Rannikko, R Valdagni, T Pickles, Y Kakehi, HG van der Poel, CH Bangma, MJ Roobol, the PRIAS study group; (V) Data analysis and interpretation: FH Drost, S Remmers, MJ Roobol; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Background: Active surveillance (AS) for low-risk prostate cancer (PCa) appears to provide excellent long-term PCa-specific and overall survival. The choice for AS as initial treatment is mainly based on avoiding side effects from invasive treatment; but AS entails regular check-ups and the possibility of still having to switch or deciding to switch to invasive treatment. Here, we assessed the long-term follow-up data from AS in real life clinical practices.

Methods: Data from the first 500 men, enrolled in PRIAS before July 2008 by 30 centers across 8 countries, were analyzed to provide long-term follow-up results. Men were advised to be regularly examined with prostate-specific antigen (PSA) tests, digital rectal examinations, and prostate biopsies. Men were advised to switch to invasive treatment if they had disease reclassification [Gleason score (GS) ≥3+4 on biopsy, more than two positive biopsy cores, a stage higher than cT2] or a PSA-doubling time of 0–3 years. We assessed time on AS, outcomes and reasons for discontinuing AS, and rates of potential unnecessary biopsies and treatments.

Results: The median follow-up time was 6.5 years. During this period, 325 (65%) men discontinued after a median of 2.3 years and 121 (24%) men had no recent (>1 year) data-update after a median of 7.3 years. The remaining 54 (11%) men were confirmed to be still on AS. Most men discontinued based on protocol advice; 38% had other reasons. During follow-up, 838 biopsy sessions were performed of which 79% to 90% did not lead to reclassification, depending on the criteria. Of the 325 discontinued men, 112 subsequently underwent radical prostatectomy (RP), 126 underwent radiotherapy, 57 switched to watchful waiting (WW) or died, and 30 had another or unknown treatment. RP results were available of 99 men: 34% to 68%, depending on definition, had favorable outcomes; 50% of unfavorable the outcomes occurred in the first 2 years. Of the 30 (6%) men who died, 1 man died due to PCa.

Conclusions: These data, reflecting real life clinical practice, show that more than half of men switched to invasive treatment within 2.3 years, indicating limitations to the extent in which AS is able to reduce the

* All contributors to the data in this paper are listed in the *Table S1*.

adverse effects of overdiagnosis. Therefore, despite guidelines stating that PCa diagnosis must be uncoupled from treatment, it remains important to avoid overdiagnosing PCa as much as possible.

Keywords: Active surveillance (AS); prostate-specific antigen screening; overdiagnosis; overtreatment; low-risk prostate cancer; limitations

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Introduction

Since the use of prostate specific antigen (PSA) testing, the majority of newly diagnosed prostate cancer (PCa) patients are considered to have low risk of progression (1). Although PSA screening leads to a PCa mortality reduction, overdiagnosis and overtreatment of these low-risk PCa patients are still a substantial concern (1-4). To prevent overtreatment, active surveillance (AS) is increasingly recognized as a favorable alternative to direct radical therapy for men with low-risk PCa (5-8). Considering all relevant data, the US Preventive Services Task Force (USPSTF) has recently proposed to endorse physicians to counsel men on PSA screening (9). This change in the USPSTF recommendation is heavily based on a modeling study which suggests that greater use of AS for low-risk PCa may tilt the balance of benefits and harms in PSA screening in favor of screening (10). However, this study models a conservative management program without considering the harms of repeated biopsies nor considering the harms of unnecessary treatments which occur despite an AS strategy. Moreover, patients who initially start an AS strategy may switch to active treatment based on signs of progression or other reasons. Furthermore, there is no consensus around the appropriate conduct of AS and differences may exist between strictly controlled cohorts and real life clinical practice (11). In this study, we analyze long-term follow-up data from the first 500 patients enrolled in the Prostate Cancer Research International Active Surveillance (PRIAS) study, representing real life clinical practice in both community and academic centers from around the world.

Methods

The PRIAS study is a prospective observational study, initiated in December 2006. It facilitates centers around the world in performing AS, by providing a web-based register (www.prias-project.org) with automatic evidence-based and individualized strategy recommendations (12). Data entering is done by each participating physician and monitored by the coordinating study center (Erasmus MC, Rotterdam, The Netherlands).

Study population

We selected the first 500 PRIAS patients, all enrolled before July 2008, to analyze their long-term follow-up data. Patients who already were under surveillance before official initiation of PRIAS were only included if the PRIAS follow-up protocol had been applied. These 500 patients have been part of previous reports (13-15).

PRIAS protocol

The recommended criteria for inclusion were Gleason score (GS) ≤3+3, stage ≤ cT2c, PSA ≤10 ng/mL, ≤2 cores positive for PCa, PSA-density ≤0.2 ng/mL/cm^3, and fitness for curative treatment (13). The recommended follow-up strategy during the first 2 years after diagnosis was a PSA test every 3 months and a digital rectal examination (DRE) every 6 months. Thereafter, a PSA test every 6 months and a DRE once yearly was recommended. Standard repeat biopsies were scheduled 1, 4, 7, and 10 years after diagnosis and subsequently every 5 years. Yearly biopsies were only recommended if PSA-doubling time (PSA DT) was between 0 and 10 years. A bone scan was recommended if the PSA level was ≥20 ng/mL. The recommended criteria to switch to active treatment were GS >3+3 or more than two positive cores on biopsy, and stage higher than cT2. A PSA DT between 0 and 3 years was used to recommend a switch to active treatment until the end of 2014, but was dropped afterwards (13). Furthermore, the criteria for a switch to active treatment were adapted to incorporate magnetic resonance imaging (MRI) targeted biopsy findings in 2015, as described in a recent publication (13).

Table 1 Patient characteristics at inclusion

Characteristics	Results
Age, years	65.9 (60.0–70.9)
PSA, ng/mL	5.3 (3.8–6.7)
Prostate volume, cm^3	42.5 (34.6–56.0)
PSA-density, ng/mL/cm^3	0.12 (0.08–0.16)
No. of biopsy cores	8 [6–10]
No. of cores positive	
1	345 (69%)
2	151 (30.2%)
>2	4 (0.8%)
Gleason score (3+3)	500 (100%)
T-stage	
cT1c	400 (80%)
cT2a	90 (18%)
cT2b	7 (1.4%)
cT2c	3 (0.6%)
Follow-up time, years	6.5 (3.1–8.4)
No. of follow-up visits	11 [5–18]

Data presented as median (IQR) or n (%). PSA, prostate specific antigen; IQR, interquartile range.

Statistical analyses

We performed descriptive statistics to report baseline characteristics, biopsy outcomes, reasons for discontinuation, treatments after discontinuation, outcomes on radical prostatectomy (RP), and biochemical recurrence (BCR), metastases and death rates. Biopsy outcomes were divided in two categories: reclassification based on GS ≥3+4 only and reclassification based on GS ≥3+4 or ≥2 cores positive. RP outcomes were divided in 4 categories: low-risk PCa (GS 3+3, ≤cT2), intermediate-risk PCa Grade Group 2 (GS 3+4, ≤cT2), intermediate-risk PCa Grade Group 3 (GS 4+3, ≤cT2), and high-risk or locally advanced PCa (GS ≥4+4 or ≥T3). BCR was defined as a PSA level ≥0.2 ng/mL after RP or a PSA level 2.0 ng/mL above the nadir after radiation therapy (RT).

Results

The first 500 patients included in PRIAS were followed prospectively by 30 centers across 8 countries (*Table S2*) until November 20, 2017. At diagnosis, the median age was 65.9 years, the median PSA was 5.3 ng/mL, and most patients had one positive biopsy core (69%) with GS 3+3 (100%) and a clinical stage T1c (80%) (*Table 1*). Fifteen patients (3%) did not comply to the recommended inclusion criteria and either had a PSA-density just above 0.2 ng/mL/mL, a PSA just above 10 ng/mL or 3 cores positive for GS 3+3.

During follow-up, a total of 838 biopsies sessions were performed in 427 patients, of which 48% underwent 2 or more surveillance biopsies (range 1–5). Of the remaining 73 patients who did not have a surveillance biopsy, 50 patients discontinued AS based on protocol advice (rising PSA, n=28), anxiety (n=15) or unknown reason (n=7); and 23 patients were lost to follow-up after a median of 3.4 years. Based on the criteria GS ≥3+4 or >2 cores positive, 79% of the 838 biopsies did not lead to reclassification; based on the criterion GS ≥3+4, 90% of the biopsies would not have led to reclassification (*Figure 1*).

The median follow-up time, the time between first and last visit, was 6.5 years. After 5 and 10 years of follow-up, respectively, 224 (45%) and 68 (13.6%) patients were still on AS; 181 (36%) and 200 (40%) patients discontinued AS based on protocol advice; 39 (8%) and 48 (9.6%) patients discontinued due to anxiety, on own request or other reasons; 14 (3%) and 19 (3.8%) patients discontinued and were lost to follow-up; 20 (4%) and 55 (11%) patients were switched to watchful waiting (WW) or died; and 22 (4%) and 110 (22%) patients had no recent (>1 year) data-update (*Figure 2*).

Among the 500 patients, 325 (65%) discontinued AS after a median of 2.3 years. Subsequently, 112 patients underwent RP, 126 underwent radiotherapy, 57 switched to WW or died, and 30 had another or unknown treatment. RP results of 99 patients were available for analysis. Of the 99 patients, 34% of patients had low-risk PCa (GS 3+3, ≤ cT2) and 33% of patients had intermediate-risk PCa Grade Group 2 (GS 3+4, ≤ cT2), 7% of patients had intermediate-risk PCa Grade Group 3 (GS 4+3, ≤ cT2), and 25% of patients had high-risk or locally advanced PCa (GS ≥4+4 or ≥ T3). Of the patients in the latter two groups, 62.5% had their active treatment within the first 2 years (*Figure 3*).

Of the total 500 patients, 16 (3.2%) patients had BCR after a median of 2.8 years after RT (n=4) and RP (n=12). Four (0.8%) patients developed metastasis after a median of 1.6 years after discontinuing AS (2 patients had switched to RP, 1 to RT, and 1 to WW). Of the 30 (6%) patients who

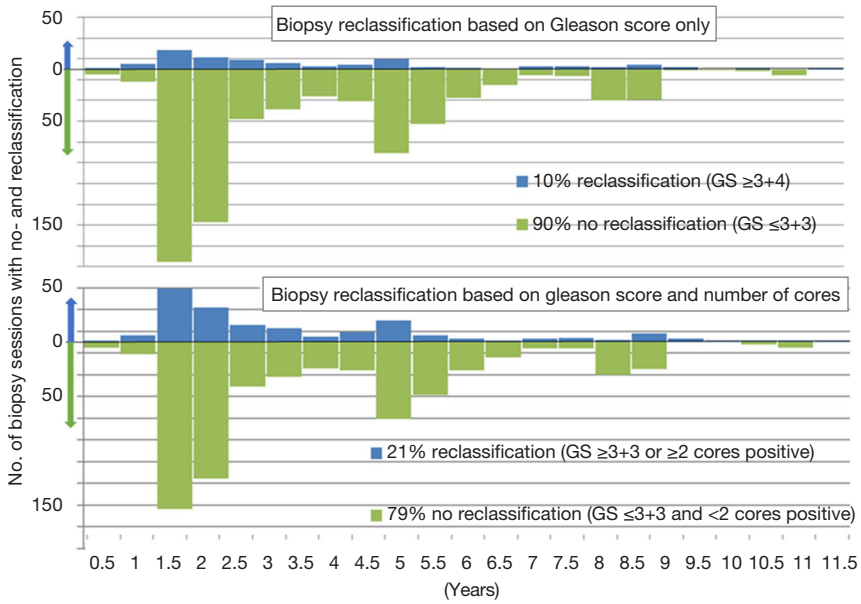
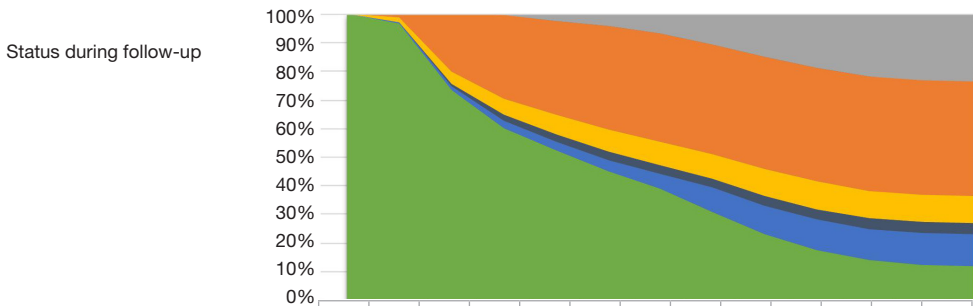


Figure 1 Biopsy reclassification during follow-up.



	Year 0	1	2	3	4	5	6	7	8	9	10	11	12
Still on AS	500	483	366	300	260	224	194	154	115	86	68	61	58
Discontinued: watchfull waiting or died	0	1	6	13	16	20	26	42	49	54	55	55	56
Discontinued: lost to follow-up	0	1	5	10	12	14	14	15	17	18	19	19	19
Discontinued: anxiety, patient request, other	0	8	22	29	35	39	42	44	47	48	48	48	48
Discontinued: based on protocol (GS ≥3+4, >2 cores positive, PSA-DT 0-3 yrs, >T2c)	0	7	101	145	163	181	189	192	196	199	200	200	201
>1 year no data update	0	0	0	3	14	22	35	53	76	95	110	117	118

Figure 2 Status during follow-up. AS, active surveillance.

died, after a median of 4.8 years after diagnosis, 1 patient died due to PCa.

Discussion

AS is increasingly being used and is considered a solution to the widely recognized problem of overtreatment of screening detected low-risk PCa (8,9,16). The mortality outcomes of AS patients seem comparable to patients who choose direct radical treatment, but possibly with a higher risk of metastasis (17-19). Although evidence is not yet conclusive, these findings have led to several guidelines endorsing PSA screening and statements that overdiagnosis does not necessarily lead to overtreatment

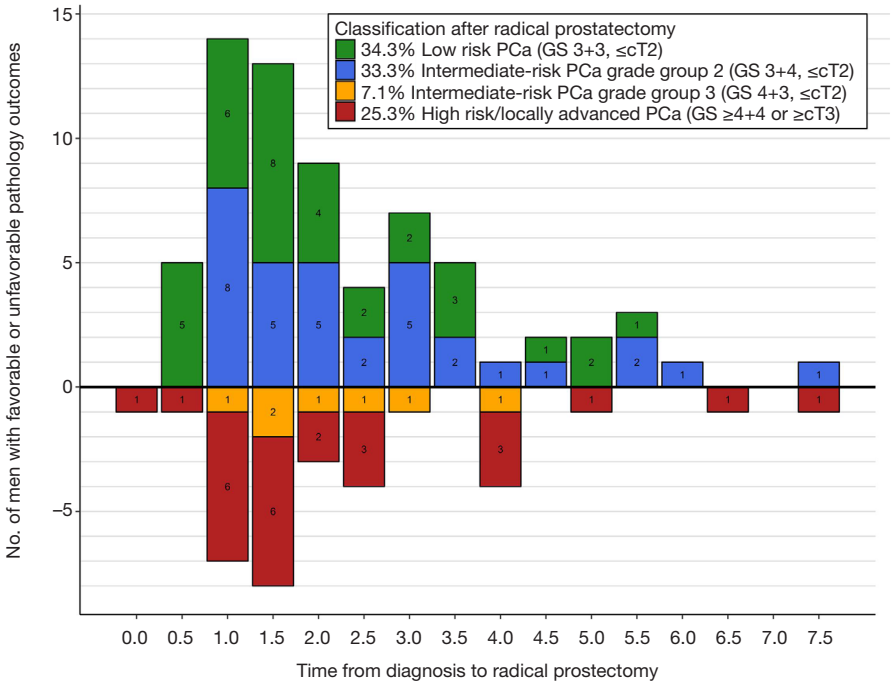


Figure 3 Radical prostatectomy results during follow-up. PCa, prostate cancer; GS, Gleason score.

when AS is used (9,20).

In this study, we show that AS indeed seems a safe alternative to direct radical therapy, with only 3.2% of patients having BCR after a switch to radical treatment, 0.8% of patients developing metastasis after discontinuing AS, and only one PCa death. However, there are some substantial drawbacks with AS which limit its capability to mitigate all harms associated with overdiagnosing low-risk PCa. In this current analysis, we found that at least 79% of surveillance biopsy sessions performed during follow-up can retrospectively be considered redundant, as they did not show reclassification. During this time period, the criteria for reclassification on biopsy were GS ≥3+4 or ≥2 cores positive. However, in 2016 the PRIAS study omitted the ≥2 positive cores criteria for reclassification because it did not significantly predict unfavorable outcomes on RP (13). Therefore, retrospectively, the 90% of biopsy sessions without GS ≥3+4 can be considered redundant. Other AS cohorts show similar high rates of biopsy sessions which did not lead to reclassification based on the criteria of GS ≥3+4 (21,22). Following a prostate biopsy, 0.5% to 6.9% of patients require hospital admission due to severe urinary tract infection or sepsis, and up to 25% experience other complaints (23), demonstrating that prostate biopsies should be avoided as much as possible.

Furthermore, of the 99 patients who underwent RP, we found that at least one third of patients had favorable pathology (GS3+3, ≤ pT2) which even if left untreated, would not progress (24). Another third of patients appeared to have intermediate risk PCa Grade Group 2 (GS 3+4, ≤ pT2), for at least some of whom it remains unclear whether they will have benefit from their switch to RP (25). The remaining one third of patients had unfavorable pathology (GS ≥4+3 or ≥ pT3), for whom a switch to active treatment was appropriate. However, as more than half of these patients had their RP within 2 years after diagnosis, we can assume that these patients were misclassified at diagnosis. As shown in previous analyses of PRIAS patients and other AS cohorts, risk stratification during AS lacks specificity to detect progression or misclassification within the window of curability, with under- and overtreatment as a result (13,26).

Finally, after 5 and 10 years of follow-up, respectively, 51% and 64% of the 500 patients had discontinued AS. Ten years after diagnosis, only 14% of the patients who originally started AS were confirmed to be still on AS. Of the remaining 22% of patients, no recent update (>1 year) was available, and these patients should be considered lost

to follow-up with the possibility of actually still being on AS or in the meantime having discontinued AS. In other AS cohorts, higher rates of patients still being on AS are reported, with 50% to 63.5% after 10 years (17,18,27), possibly explained by differences in inclusion and follow-up criteria, and the less strictly controlled PRIAS protocol. Moreover, not all patients who switch to active treatment do so because of protocol based signs of progression. In this study, 48 (18%) of patients switched to active treatment because of anxiety or other reasons, comparable to the 23% of patients in the Johns Hopkins cohort (18).

This study has some limitations inherent to the initial facilitating setup of this observational study. Some men, for example, were lost to follow-up or did not have a recent data-update. As this is not a strictly controlled cohort, events might have occurred out of our scope. Furthermore, during the follow-up period of these patients, MRI was largely unavailable. Although MRI is more frequently used in contemporary AS strategies, including PRIAS, more data and longer follow-up are needed to evaluate the additional value of MRI in AS to detect misclassification and especially to detect progression (28-30). At least for now, MRI is not accurate enough to replace systematic re-biopsies (31). Future ways to improve the conduct of AS most likely involve incorporation of more sophisticated individualized risk stratification methods, based on MRI and other biomarkers (32,33).

Based on our findings here, however, AS seems not to solve the problem of overtreatment sufficiently. Therefore, improvement of the diagnostic pathway is an absolute must. With PSA-based screening, benefits (mortality reduction) and harms (unnecessary testing and overdiagnosis) go hand in hand (34). These harms could, however, be reduced by smarter screening using risk prediction tools to aid in the decision to have a PSA-test or to undergo a prostate biopsy (35). In addition, other biomarkers and MRI could be incorporated into the diagnostic pathway to secure the detection of potentially lethal PCa (36,37).

Conclusions

Although AS seems a favorable alternative to direct radical therapy for men with low-risk PCa, the ability of AS to prevent the harms associated with overdiagnosis has not yet been clearly defined in practice. During AS, despite its aim, many in retrospect-unnecessary biopsies are performed and risk stratification methods lack the specificity to prevent all of the overtreatment. Therefore, it remains important to avoid overdiagnosing PCa as much as possible.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The medical ethical committee of the Erasmus University Medical Centre and, dependent of local regulations, local committees, approved the PRIAS study (MEC number 2004-339). All participants provided written informed consent.

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Supplementary

Table S1 List of PRIAS study group members, contributing to the data in this paper, by medical center

Center	Country	Members
Admiraal de Ruyter Ziekenhuis te Goes/Vlissingen	Netherlands	Dr. F.M. Bentvelsen
Admiraal de Ruyter Ziekenhuis te Goes/Vlissingen	Netherlands	Dr. J. Jaspars
Albert Schweitzer Ziekenhuis	Netherlands	Dr. R.M. Potjer
Albert Schweitzer Ziekenhuis	Netherlands	Dr. Rene Raaijmakers
Albert Schweitzer Ziekenhuis	Netherlands	Dr. W.M. Stomps
Albert Schweitzer Ziekenhuis	Netherlands	Dr. J.J. Vis
Albert Schweitzer Ziekenhuis	Netherlands	Dr. P.A. Wertheimer
Albert Schweitzer Ziekenhuis	Netherlands	Dr. A.G.M. Zeegers
Amphia Ziekenhuis	Netherlands	Dr. P.J. van den Broeke
Amphia Ziekenhuis	Netherlands	D. van der Schoot
Amphia Ziekenhuis	Netherlands	Drs. H. Jansen
Amphia Ziekenhuis	Netherlands	Ilze van Onna
Amphia Ziekenhuis	Netherlands	Dr. E.H.G.M. Oomens
Amphia Ziekenhuis	Netherlands	Dr. P.J. Posthumus
Antoni van Leeuwenhoek Ziekenhuis (NKI-AVL)	Netherlands	E. van Muilekom
Antoni van Leeuwenhoek Ziekenhuis (NKI-AVL)	Netherlands	Dr. H. van der Poel
BC Cancer Agency	Canada	Adam Kahnamelli
BC Cancer Agency	Canada	Alex Briede
BC Cancer Agency	Canada	Dana Matuszewski
BC Cancer Agency	Canada	Henry Lau
BC Cancer Agency	Canada	Devon Poznanski
Canisius-Wilhelmina Ziekenhuis Nijmegen	Netherlands	Dr. D.M. Somford
Canisius-Wilhelmina Ziekenhuis Nijmegen	Netherlands	Dr. H. Vergunst
Catharina Ziekenhuis Eindhoven	Netherlands	Dr. E.L. Koldewijn
Catharina Ziekenhuis Eindhoven	Netherlands	Dr. P.E.F. Stijns
Catharina Ziekenhuis Eindhoven	Netherlands	Dr. Wout Scheepens
Diakonessenhuis Utrecht	Netherlands	Dr. Karin van Dalen
Diakonessenhuis Utrecht	Netherlands	Roan Spermon
Emco Klinik, Salzburg	Austria	Dr. Andreas Jungwirth
Erasmus MC	Netherlands	Dr. W. Boellaard
Erasmus MC	Netherlands	Dr. J. Boormans
Erasmus MC	Netherlands	Dr. M.Busstra
Erasmus MC	Netherlands	Prof. Dr. F.H. Schröder
Erasmus MC	Netherlands	Dr. W. Kirkels
Erasmus MC	Netherlands	Dr. Meelan Bul
Erasmus MC	Netherlands	Dr. P. Verhagen
Erasmus MC	Netherlands	Dr. Marij Dinkelman-Smit
Erasmus MC	Netherlands	Wouter Roobol
Erasmus MC	Netherlands	L.D.F. Venderbos
Erasmus MC	Netherlands	A.R. Alberts
Erasmus MC	Netherlands	F-J. H. Drost
Hospital Virgen del Camino, Pamplona	Spain	Manuel Montesino
Kuopio University Hospital	Finland	Sirpa Aaltomaa
Krankenhaus der Barm. Brueder	Germany	Prof. Nikolaus Schmeller
Maasstad Hospital Rotterdam	Netherlands	Dr. D.C.D. De Lange
Maasstad Hospital Rotterdam	Netherlands	Dr. D. van den Ouden
Medisch Spectrum Twente	Netherlands	Drs. Emile Alleman
Medisch Spectrum Twente	Netherlands	Drs. Boudewijn Santerse
Medisch Spectrum Twente	Netherlands	Dr. Henriette Leenknegt
Medisch Spectrum Twente	Netherlands	Dr. Maarten-Jan Pit
Medisch Spectrum Twente	Netherlands	Sing Khoe
Oulu University Hospital	Finland	Pekka Hellström
Reinier de Graaf Gasthuis	Netherlands	J. Hoeven
Rivas Care Group	Netherlands	Dr. R. Gilhuis
Rivas Care Group	Netherlands	Dr. H. Plancke
SIURO - Fondazione IRCCS Istituto	Italy	Tiziana Magnani
SIURO - Fondazione IRCCS Istituto	Italy	Maria Francesca Alvisi
SIURO - Fondazione IRCCS Istituto	Italy	Tiziana Rancati PhD
SIURO - Fondazione IRCCS Istituto	Italy	Silvia Catania
St. Franciscus Gasthuis	Netherlands	Dr. M. Asselman
St. Franciscus Gasthuis	Netherlands	Dr. Ilse van den Berg
St. Franciscus Gasthuis	Netherlands	Dr. J. Blom
St. Franciscus Gasthuis	Netherlands	Dr. E. Boevé
St. Franciscus Gasthuis	Netherlands	Dr. R. Nooter
St. Franciscus Gasthuis	Netherlands	Dr. J. Rietbergen
St. Franciscus Gasthuis	Netherlands	Dr. Stijn de Vries
University Hospital Muenster	Germany	Barbara Thielen
University Hospital Muenster	Germany	Dr. Sebastian Kemper
University Hospital Muenster	Germany	Klaus Kruse
University Hospital Muenster	Germany	Dr. A. Semjonow
University Hospital Muenster	Germany	Thomas Köpke
Universitair Ziekenhuis Gent	Belgium	Prof. W. Oosterlinck
Vlietland Ziekenhuis	Netherlands	Drs. Ilse van den Berg
Vlietland Ziekenhuis	Netherlands	Drs. Helene Wilkens
VU Medical Center Amsterdam	Netherlands	Dr. A.N. Vis
Westfries Gasthuis	Netherlands	Dr. Maicle Leter
Ziekenhuis Bernhoven	Netherlands	A.Q.H.J. Niemer
Ziekenhuisgroep Twente	Netherlands	Dr. E.B. Cornel
Ziekenhuisgroep Twente	Netherlands	Gerd-Jan Molijn

Table S2 Inclusions per center

Country	Center	Inclusions
The Netherlands	Erasmus University Medical Center, Rotterdam	84
	Netherlands Cancer Institute, Amsterdam	54
	St. Franciscus Hospital, Rotterdam	48
	Hospital group Twente, Enschede	30
	Albert Schweitzer Hospital, Dordrecht	44
	Admiraal de Ruyter Hospital, Goes	21
	Reinier de Graaf Hospital, Delft	14
	Medisch Spectrum Twente, Enschede	9
	Amphia Hospital, Breda	7
	Canisius-Wilhelmina Hospital, Nijmegen	7
	Vlietland Hospital, Rotterdam	7
	Hospital Bernhoven, Uden	5
	Diakonessenhuis, Utrecht	4
	VU University Medical Centre, Amsterdam	4
	Ikazia Hospital, Rotterdam	2
	Maasstad Hospital Rotterdam, Rotterdam	2
	Rivas Care group, Gorinchem	2
	Westfries Hospital, Hoorn	2
	Catharina Hospital, Eindhoven	1
	Ruwaard van Putten Hospital, Spijkenisse	1
Finland	Helsinki University Central Hospital, Helsinki	66
	Kuopio University Hospital, Kuopio	1
	Oulu University Hospital, Päijät-Häme	1
Canada	British Columbia Cancer Agency, Vancouver	38
Italy	Fondazione IRCSS Istituto Nazionale dei Tumori, Milan	28
Germany	University Hospital Muenster, Muenster	6
	Krankenhaus der Barmherzige Brüder, Munich	2
Spain	Hospital Virgen del Camino, Pamplona	5
Austria	Emco Klinik, Salzburg	4
Belgium	University Hospital Gent, Gent	1